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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/686,782 | 10/17/2003 | Harald W. Sontheimer | 2006636-0064 | 7705 |

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| EXAMINER | |
|---|---|
| CHEN, SHIN LIN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1632 | |

DATE MAILED: 11/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/686,782 | SONTHEIMER ET AL. | |
| | Examiner | Art Unit | |
| | Shin-Lin Chen | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *15 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1 and 15-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 15-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Applicants' amendment filed on 9-15-06 has been entered. Claims 1, 26 and 27 have been amended. Claims 1 and 15-28 are pending and under consideration.

### *Double Patenting*

1. Applicant is advised that should claim 22 be found allowable, claim 28 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

2. Applicant is advised that should claim 1 be found allowable, claims 26 and 27 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

3. Applicant is advised that should claim 20 be found allowable, claim 21 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Applicants' statement that those objections will be addressed and/or explained as to the improper objection according upon indication of allowability of the claims (amendment, p. 5) is acknowledged.

***Claim Rejections - 35 USC § 112***

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1 and 15-28 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention and is repeated for the reasons set forth in the preceding Official action mailed 3-28-06. Applicant's arguments filed 9-15-06 have been fully considered but they are not persuasive.

Applicants argue that protein and peptide biotherapies have been approved and used as successful therapies for many years, for example, insulin, erythropoietin and monoclonal antibodies. Applicants further argue that protein therapy and gene therapy are not parallel and difficulties in gene therapy do not transfer directly to protein therapies (amendment, p. 6-7). This is not found persuasive e because of the reasons set forth in the preceding Official action mailed 3-28-06. Although it was known in the art for how to make a recombinant protein or peptide, however, the art or protein therapy was unpredictable at the time of the invention. The administration route, the location of the target cells, the stability of the polypeptide, and the

amount of the polypeptide that reaches the target site would determine the efficiency of protein transfer and whether said protein can provide therapeutic effect for a particular disease in vivo. There are various barriers before a protein can reach its target cells, for example, layers of dermal cells, blood vessel wall cell membranes, proteases and lysosomal degradation within cells, extracellular matrix between cells, and gastrointestinal digestive acids, and there is blood-brain barrier for treating brain tumors. Whether sufficient chlorotoxin-cytotoxic protein moiety would reach target neuroectodermal tumor in a subject to provide therapeutic effect depends on the concentration of the chlorotoxin complex used, the administration route, the location of the target cells and the stability of the polypeptide etc. Further, the claims encompass treating various neuroectodermal tumors by administering a pharmaceutical composition comprising a chlorotoxin fused to any cytotoxic moiety or cytotoxic moiety recited in claim 15, i.e. gelonin, ricin, saponin, pseudomonas exotoxin, pokeweed antiviral protein, diphtheria toxin, or any complement protein, via various administration routes so as to provide therapeutic effect for treating said neuroectodermal tumor in vivo. Different neuroectodermal tumors differ from each other physiologically, morphologically and pathologically. Different cytotoxic moieties fused to chlorotoxin differ from each other in their cytotoxic activity toward different neuroectodermal tumors. Therefore, treatment of different neuroectodermal tumors with different cytotoxic moieties has to be considered individually. The doses and schedules used and administration route could differ dramatically depending on the type of cytotoxic moiety used and the type of neuroectodermal tumor treated. The specification fails to provide adequate guidance and evidence for how to treat various neuroectodermal tumors in the brain by using a pharmaceutical composition comprising a chlorotoxin fused to any cytotoxic moiety via various administration

routes so as to provide therapeutic effect in vivo. Thus, one skilled in the art at the time of the invention would require undue experimentation to practice over the full scope of the invention claimed.

Applicants argue that determination of effective doses, protein half life and delivery are routine procedures and would not require undue experimentation for one of skilled in the art. Applicants cite reference Veiseh and argue that blood-brain barrier would not be a concern for chlorotoxin and chlorotoxin fusions (amendment, p. 7). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 3-28-06 and the reasons set forth above. Veiseh teaches using near infrared (NIR) chlorotoxin-based probe to detect medulloblastoma tumors after systemic administration of the probe in 2 mouse model without surgical disruption of the blood brain barrier. The NIR chlorotoxin-based probe is used as a **detection probe** NOT as an agent to **treat** various neuroectodermal tumors. A successful detection of a medulloblastoma tumor with NIR chlorotoxin-based probe does not mean that any cytotoxic moiety fused to chlorotoxin would be able to treat numerous different neuroectodermal tumors in a subject. There is no evidence of record that any cytotoxic moiety fused to chlorotoxin would be able to treat numerous different neuroectodermal tumors in a subject. Further, Veiseh does not disclose what is attached to the NIR chlorotoxin-based probe, maybe the NIR chlorotoxin-based probe can pass through blood brain barrier but there is no evidence of record that shows chlorotoxin fused to various cytotoxi moiety, such as different proteins, can pass through the blood brain barrier. Thus, it is still unclear whether chlorotoxin-cytotoxic moiety complex can pass through blood brain barrier in a subject.

Applicants argue that the present claims are directed to methods of using a composition comprising a fusion of chlorotoxin with a cytotoxin having known sequences and known function, therefore, the combination of chlorotoxin fused to a cytotoxic moiety is routine experimentation to one of skilled in the art (amendment, p. 8). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 3-28-06. The claims read on using any cytotoxic moiety to treat numerous different neuroectodermal tumors. The phrase "cytotoxic moiety" is very broad that would encompass any protein or peptide or any molecule that is cytotoxic. Therefore, the claims encompass using proteins or peptides having unknown amino acid sequences and biological functions, and the biological function of a protein was unpredictable from mere amino acid sequence at the time of the invention. Even the recited different toxins, antiviral proteins, and complement proteins have different amino acid sequences and different biological functions and whether they would able to treat different neuroectodermal tumors in vivo was unpredictable at the time of the invention. The dose of the cytotoxic moiety, the stability of said cytotoxic moiety during protein transfer in vivo, and the effect of the cytotoxic moiety on treating neuroectodermal tumor all vary among different cytotoxic moieties, however, the specification fails to provide such specific guidance for those various cytotoxic moieties recited in the claim. Thus, one skilled in the art would not know how to treat numerous neuroectodermal tumors in vivo by using various chlorotoxin-cytotoxic moiety complexes via various administration routes so as to provide therapeutic effect for treating said neuroectodermal tumor.

***Conclusion***

No claim is allowed.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER